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CLINICAL MEDICINE
ANTIBIOTICS AS CHEMOTHERAPEUTIC AGENTS — *Selman A. Waksman*

LEGAL MEDICINE
AUTOPSIES MEDICO-LEGAL IMPORTANCE — *Louis J. Gelber*

PAN AMERICAN MEDICAL WOMAN'S SECTION
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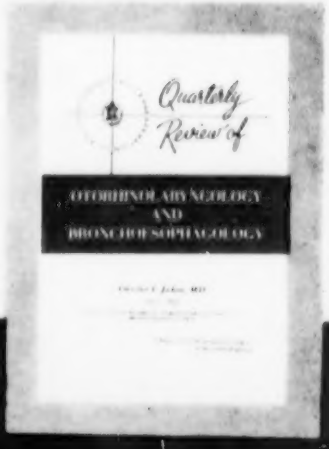

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1. Stone, A.: The Prevention of Conception, in Fishbein, M., and Burgess, E. W.: Successful Marriage, Garden City, N. Y., Doubleday & Company, 1947, pp. 279-80.
2. Stromme, W. B., and Rathnam, M. S.: Clinical Experience with a New Gel Alone Method of Contraception, World Population Problems and Birth Control, Ann. New York Acad. Sc. 54:83 (May) 1952.
3. Hunter, G. W., Darner, C. B., and Gilliam, J. S.: A Method of Contraception Without Diaphragm — A Two Year Investigation, World Population Problems and Birth Control, Ann. New York Acad. Sc. 54:825 (May) 1952.
4. Talladega County Health Department, Alabama: Unpublished Data, March 1952.

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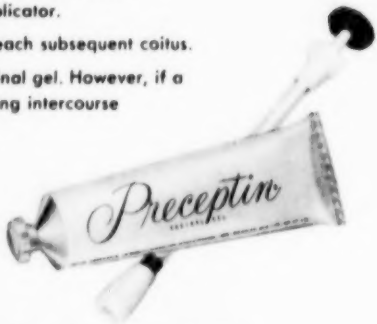

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INTERNATIONAL RECORD OF MEDICINE

Clinical Medicine

Antibiotics as Chemotherapeutic Agents 41
Selman A. Waksman

Legal Medicine

Autopsies—Medico-Legal Importance 53
Louis J. Gelber

Medical Woman's Section

Treatment of Hemorrhagic Disorders in Infants and Children 56
I. Newton Kugelmass

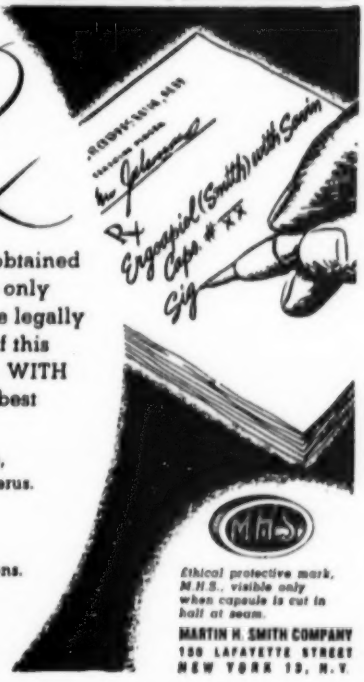
GENERAL PRACTICE CLINICS

Abstracts

Overnutrition and Obesity 63
Alcoholism as a Nutritional Problem 63
Effects in Rheumatoid Arthritis of Hydrocortisone and Cortisone Injected Intra-Articularly 64
Dietary Treatment of Hypertension 65
Puncture of Goiters for Aspiration Biopsy 65

Book Reviews

Abundant Life, A Doctor Speaks of Health 66
Applied Physiology 66



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VOLUME 12 NO. 1 **FEBRUARY 1953**

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Acute Bronchopulmonary Suppuration: Therapy with Endoscopic Application of Oleaginous Penicillin 69
A. *Albert Carabelli*

Abstracts

Otology

Secretory Otitis Media 73

Recruitment and Speech Discrimination Loss 74

Otitis Media: The Practitioner's Responsibility 74

Local Injection of Procaine Solution in Secondary Mastoiditis 75

Further Observations Concerning the Toxic Effects of Streptomycin and Quinine on the Auditory Organ of Guinea Pigs 76

Ménière's Syndrome as a Premonitory Symptom of Cerebrospinal Vascular Occlusion: A Report of Two Cases 76

Deafness—Its Present Day Management 77

Deafness Following Mumps: Rehabilitation 77

Ventriculomastoid Shunt in the Management of Obstruction to the Aqueduct of Sylvius in the Adult: Report of a Case 78

Laryngology

Progress in the Surgical Treatment of Bilateral Laryngeal Paralysis 79

Left Recurrent Laryngeal Nerve Paralysis in Arteriosclerotic Heart Disease 80

An Afferent Representation of the Larynx in the Cerebellum 80

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1. Steinbrocker, O.; Berkowitz, S.; Ehrlich, M.; Elkind, M., and Carp, S.: Paper read before the Annual Meeting of the American Rheumatism Association, Chicago, Ill., June 6, 1952.

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RECORD OF MEDICINE

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Antibiotics as Chemotherapeutic Agents*

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NEW BRUNSWICK, N. J.

INTRODUCTION

In the history of man's struggle against infectious diseases and epidemics, certain great discoveries stand out as landmarks. By far the most important of these was the recognition of the fact that bacteria and other microorganisms are the responsible infectious agents. The ancients designated as pests, plagues, or pestilences, diseases that were epidemic in nature and that were frequently ascribed to the wrath of the Gods. Gradually it became recognized that such diseases are due to infectious agents, although it was only during the latter part of the last century that the microbial origin of disease became firmly established.

It would be difficult to list the investigators who are responsible for the various discoveries in this field. It is sufficient to list three important contributions.

Louis Pasteur stands out as the central figure in this great advance of human knowledge and of improvement of human and animal health. It was he who emphasized time and again the role of different microbes as causative agents of infectious diseases. Numerous efforts were soon made to correlate the occurrence and distribution of bacteria and other microorganisms with specific diseases. Experimental procedures were devised for studying the causation of disease and for producing various biologic and chemical agents for the control of infectious diseases.

Robert Koch, discoverer of the causative agent of tuberculosis is another outstanding investigator in this field of research. His contribution to the life cycles of bacteria and his methods for isolation, cultivation, and staining of bacterial agents have served further to advance this field of knowledge. Numerous other investiga-

*Journal Series Paper, Department of Microbiology, Rutgers University—the State University of New Jersey.

tors, including not only bacteriologists, but also protozoologists, mycologists, and virologists, made further contributions toward the elucidation of the role of various microorganisms in the causation of disease and their mode of transmission.

The recognition of specific microbes as responsible agents for particular diseases was immediately followed by a search for chemical substances or drugs which could be used in the treatment of such diseases. Paul Ehrlich, noted for his contributions to immunology, is usually credited with being the "father of chemotherapy." He first established the great potentialities of arsenicals, notably salvarsan, in combating syphilis. The medical world became aroused at once. It was hoped that before very long new drugs would be found that would act in a similar manner upon bacterial and other diseases. Unfortunately, bitter disappointment soon followed when no other drugs of any importance immediately followed the discovery of salvarsan. This led to the conclusion that whereas infections caused by protozoans and by spirochetes may be treated with chemical drugs, true bacterial infections remain resistant to chemotherapy.

It took a quarter of a century before another group of chemical compounds was introduced, which proved to be highly effective against bacterial infections. Introduction of these compounds resulted in a new era in chemotherapy. This occurred only about 17 years ago with the discovery of sulfanilamide and other sulfa drugs. It was thus established beyond question that not only protozoan but also bacterial infections lend themselves readily to generalized treatment with chemical drugs. Thus the basis was laid for true bacterial chemotherapy. However, there still remained a great many diseases which did not respond to the sulfa drugs, including those that are caused by various gram-negative bacteria, tuberculosis, and virus diseases. Furthermore, the sulfa compounds were not ideal chemotherapeutic agents, since they often caused toxic reactions and under certain conditions gave rise to drug-resistant strains of bacteria. It gradually came to be recognized, therefore, that these compounds were not the final answer to the control of microbial infections of man and animals.

Even before the above conclusion could be reached, a dramatic advance in chemotherapy was made through microbiologic research, which led to the discovery of antibiotics. The whole problem of chemotherapy immediately took on a totally different aspect. Diseases that were never before believed to be susceptible to therapy were treated with remarkable effectiveness. Old drugs were replaced by new ones, which were more effective and less toxic. It is no wonder, therefore, that a leading physician spoke not so long ago of the present period as the "age of antibiotics." One of the most important chapters in the history of science and medicine is being written before our very eyes, and microbiology has entered a new phase of development.

To conclude this brief survey, it is sufficient to add that the chemical synthesis of new compounds has now gained added stimulus, and new methods of approach to the therapy of disease are being constantly developed. Some of the antibiotics are being synthesized, and thus new information is being gained in the ever-expanding battle against infectious diseases of man and animals.

ANTAGONISMS

Although the phenomenon of antagonism or antibiosis among microorganisms has been frequently observed since the early days of bacteriology and mycology, and although the ability of various bacteria and fungi to produce antibacterial substances has been thoroughly appreciated, recognition of the great chemotherapeutic potentialities of these substances, later designated as "antibiotics," is of very recent origin. Only a dozen years ago, antibiotics were spoken of as lysins, toxins, bacteriolysins, bacteriotoxins, bacteriostatics, bactericidal and bacteriolytic substances, antibacterial or antagonistic agents, lethal and staling principles. One hardly thought of them in terms of chemotherapeutic significance. At best, such practical applications were thought to be of limited importance, and, at worst, these phenomena were looked on as mere microbiologic or clinical curiosities.

The nature of the mechanisms responsible for the antagonistic properties of microorganisms and their significance in the growth and nutrition of the organisms producing them, on the one hand, and of the organisms against which they were effective, on the other, were highly confused. This confusion contributed further to a complete lack of recognition of their potential importance in human and animal therapy. To illustrate this, it is sufficient to draw attention to the investigations of Alexander Fleming in 1929 and of Richard Weindling in 1933, dealing with two such substances, penicillin and gliotoxin. Neither of these investigators considered the immense importance of these products as potential chemotherapeutic agents. This was true also of the numerous studies of the antibacterial substances produced by certain gram-negative and spore-forming bacteria, the former including such important substances as pyocyanase, and the latter a variety of preparations obtained from specific bacteria, notably *Bacillus subtilis* and *B. mycoides*. Even less can be said of products of *Actinomycetes*, of which only two enzyme-like preparations were recognized. As late as 1939, neither of these substances of microbial origin received general consideration as promising therapeutic potentialities and as potential precursors of a new era in medicine.

Our modern knowledge of the production and utilization of antibiotics dates back only to the last decade. The isolation of gramicidin and tyrocidine from a spore-forming soil bacterium in 1939 was soon followed by the reisolation of penicillin, and by the demonstration of the great potentialities of *Actinomycetes* as producers of antibiotics. These contributions have opened a new chapter in microbiology and especially in human and animal therapy. In this brief time, more than three hundred different compounds and preparations now designated as antibiotics have been isolated and tested for their antimicrobial properties. Hundreds of thousands of cultures representing numerous groups of microorganisms, largely bacteria, fungi, and *Actinomycetes*, have been isolated from fresh soil and from other natural substrates or were taken from various culture collections. These microorganisms have been examined for their ability to inhibit the growth of pathogenic bacteria, fungi, viruses, and protozoa. They have been further studied for their capacity to produce antibiotic substances which would possess the same property. The literature of penicillin alone has expanded from four to five papers, published prior to 1939, to

many thousands of articles and numerous volumes written in many languages. Streptomycin, the isolation of which was announced only about 8 years ago, is already covered by a voluminous literature of nearly 6,000 papers and by a number of volumes. Other antibiotics, notably bacitracin, chloramphenicol, aureomycin, terramycin, and neomycin, have taken an important place in the treatment of numerous infectious diseases caused by bacteria, fungi, spirochetes and protozoa, rickettsiae, and certain viruses. Numerous other compounds loom on the horizon as promising therapeutic agents.

WHAT ARE ANTIBIOTICS?

One may now define the nature and properties of antibiotics. They are produced by microorganisms growing in artificial media, and have the capacity to inhibit the growth of, and even to destroy, various bacteria and other microorganisms in dilute solutions. They are thus distinctly different from plant and animal products that may possess similar properties and from microbial products (acids and alcohols) that are active only in high concentrations. Antibiotics represent a wide variety of chemical compounds, which differ greatly in their selective action upon different microorganisms, in their specific toxicity to animals, and in their activity in the human and animal body. Literally thousands of laboratories in this country and abroad are now engaged in the search for new antibiotics which would be effective against those diseases that are now resistant to, or insufficiently affected by, the substances already known.

One may actually lay down certain rules or principles which would have to be recognized before a new antibiotic can qualify as a suitable chemotherapeutic agent. It must possess certain well-defined properties, as follows:

1. It must be selective in its action against various microorganisms, and should preferably not be a generalized protoplasmic poison.

2. It must be effective against those microorganisms that are not subject as yet to the action of antibiotics, or it must be more effective than the agents now known.

3. It must exert its antimicrobial activity in the presence of body fluids.

4. It should not be inhibited by substances present in the blood and should not be destroyed by tissue enzymes.

5. It should be well tolerated when injected into animals in amounts required to combat infections.

6. It should not damage the leukocytes in the blood in concentrations necessary to affect the infectious agent, and should not be injurious to body tissues.

7. It should be excreted readily, but not too rapidly, from the animal body, and should not accumulate and produce undesirable after-effects.

8. It should not favor the rapid development of resistance among sensitive organisms.

The potential synergistic properties of a new antibiotic with another antibiotic or with a synthetic compound must not be overlooked, even though the new agent may not in itself play an important role in chemotherapy.

The various antibiotics so far isolated and recognized can be classified on the basis of their chemical composition, their antimicrobial spectra, their toxicity to animals, or their chemotherapeutic potentialities.

Chemically, antibiotics range from fairly simple to highly complex compounds. Some of them contain carbon, hydrogen, and oxygen; these include such relatively simple compounds as kojic acid ($C_6H_6O_4$) and clavacin ($C_7H_6O_4$). Others are more complex and contain nitrogen, such as streptomycin ($C_{21}H_{37}O_{12}N_7$), or nitrogen and sulfur, such as penicillin ($C_9H_{11}O_4SN_2R$), or nitrogen and chlorine, such as chloramphenicol ($C_{11}H_{12}O_5N_2Cl_2$). The most complex substances comprise the polypeptides, such as gramicidin, subtilin, and bacitracin, and the proteins, such as the colicins. Only three antibiotics so far have been synthesized, namely, penicillin, clavacin, and chloramphenicol; of these, only the last one has found practical application in therapy. Some of the antibiotics represent single chemical entities, as most of those listed above. Others are made up of several closely related compounds; this is true of the several penicillins, of the streptomycins, and of A-T complex, comprising aureomycin and terramycin. The individual entities may vary in their antimicrobial spectra, in toxicity to animals, in stability, and *in vivo* activity.

Microbiologically, the antibiotics also vary greatly. This is best illustrated by their respective antimicrobial spectra. Clavacin has a very wide spectrum, affecting numerous bacteria and fungi. Bacitracin and penicillin have much narrower spectra, since they are not active upon fungi and viruses and have little activity upon various gram-negative bacteria and the tuberculosis organism. Streptothricin, streptomycin, and neomycin are active against both gram-negative and gram-positive bacteria. Chloramphenicol, aureomycin and terramycin are also active against the rickettsiae and some of the larger viruses. Some antibiotics possess only very narrow spectra, as the colicins, which are active only against certain few strains of *Escherichia coli* and possibly upon a few other enteric bacteria. Viomycin, esperin, *Mycobacterium smegmatis* factor, and nocardin are active only upon certain mycobacteria. The polymyxins are active largely upon gram-negative bacteria. Some substances, like actidione, fradicin, fungicidin, and antimycin are active only upon fungi.

Toxicologically antibiotics vary from the least toxic penicillins to the most toxic actinomycins, streptolin, and the xanthimycins. Clinically, they vary from such important chemotherapeutic agents as penicillin, streptomycin, aureomycin, chloramphenicol, terramycin, and neomycin that are used against a great variety of infections, to compounds like tyrothricin and bacitracin which are used largely for topical applications, and to substances like the polymyxins which have only limited and specific applications.

The microorganisms which are capable of forming antibiotics frequently represent large and variable groups. This is true of the numerous members of the *Penicillium notatum-P. chrysogenum* group which yield various penicillins, the *Streptomyces griseus* group which produce streptomycin, the *S. lavendulae* group which form streptothricin and a variety of other substances, and *B. subtilis*, which is responsible for a dozen more compounds possessing antimicrobial properties. There are certain

marked differences between the various members of these groups. The numerous strains of *Penicillium* vary largely in their quantitative and qualitative production of penicillin, some cultures producing only traces of this antibiotic whereas others give rise to large quantities of it and can be utilized for large-scale manufacture. Some produce one form of penicillin, and others give rise to another. The various strains of *S. griseus* can be divided into four subgroups, on the basis of their ability to produce antibiotics: (a) those that form streptomycin or streptomycin-like substances; (b) those that form grisein or grisein-like materials; (c) those that are unable to produce either of these antibiotics, but are capable of forming various unidentified substances, some of which are active against gram-positive bacteria but not against gram-negative organisms; (d) the cultures that are unable to form any antibiotic at all, at least not in the media so far tested.

In the light of the foregoing postulates, it may be of interest to evaluate some of the antibiotics that have found practical application in chemotherapy.

Tyrothricin has a narrow antibiotic spectrum, being largely active against gram-positive bacteria and cocci. It tends to exert a hemolytic effect upon the blood. This property limits its use to topical applications and it cannot be applied parenterally or as a generalized agent. When announced by Dubos in 1939, it attracted universal attention and served as the stimulus in arousing the interest in the study of production of antibiotics and their utilization in disease control.

Penicillin is a far more effective agent than tyrothricin. It has a broader antibiotic spectrum, although it is limited largely in use against gram-positive bacteria, various cocci, spirochetes, and certain other organisms. It is far less toxic; indeed, it may be said to be one of the most nontoxic drugs known. Penicillin, first observed by Fleming in 1929 then rediscovered in 1940 by Chain and Florey, immediately filled a great need in the treatment of numerous infectious diseases afflicting man and animals. It possesses certain limitations, however, chief among which is a lack of activity against various gram-negative rod-shaped bacteria, as well as the acid-fast bacteria. Its wide use has gradually led to development of resistance among certain sensitive bacteria.

Streptomycin, discovered in 1943, tended to fill the gap left by penicillin. Although not so potent as penicillin against diseases that lend themselves to treament with penicillin, streptomycin is effective against a variety of diseases not subject previously to any form of therapy. Its greatest importance lies in its efficacy in the treatment of tuberculous meningitis and other forms of tuberculosis, as well as in the treatment of numerous infections caused by gram-negative bacteria and gram-positive bacteria resistant to penicillin. Streptomycin has certain serious limitations, chief among which is its potential causation of vestibular disturbances, its effect on the auditory system, and the rapid development of resistance among sensitive bacteria after prolonged contact.

Chloramphenicol, *aureomycin*, and *terramycin* are active not only upon various gram-positive and gram-negative bacteria, but also against rickettsiae and some of the larger viruses. They are usually administered orally and have found extensive appli-

cation in the treatment of a variety of diseases, such as typhus fever, typhoid fever, whooping cough, and trachoma.

Among the other antibiotics which have become established as chemotherapeutic agents, may be mentioned *bacitracin*, *neomycin*, and *polymyxins*. Since these compounds either tend to exert a somewhat toxic effect when parenterally administered or have a narrow spectrum, they are used topically and orally, or only for specific infections that do not lend themselves to other forms of therapy.

Since the discovery of penicillin, a fungus product, the most important antibiotics have been obtained largely from cultures of *Actinomycetes*, all from members of the genus *Streptomyces*. The bacteria, notably the spore-forming organisms, have contributed certain important agents, mostly polypeptides, some of which, such as tyrothricin, bacitracin, and polymyxins, have found certain applications in therapy. The nonspore-forming bacteria have contributed pyocyanase, one of the earliest antibiotics, and nisin, produced by a *Micrococcus;* the latter has shown certain promise in the treatment of tuberculosis. The fungi, including both the lower filamentous and the higher mushroom forms, have contributed no important agents other than penicillin, although numerous compounds were isolated and tested. Although some of these, as clitocybine and polyporin, appeared at first to be promising, they did not, on further study, find any practical application. Reports have also appeared recently about the potential value of extracts of *Psalliota campestris*, the common edible mushroom, in the treatment of cancer; further and more accurate studies are required, especially in the treatment of a group of diseases which arouse much attention and for which proper evaluation is not always easy.

APPLICATIONS OF ANTIBIOTICS

Antibiotics have now found extensive applications in the treatment of numerous infectious diseases and in various fields where selective antimicrobial agents are desirable. Among the latter, mention may be made of their use in the purification of viruses, in the preservation of animal semen, and in the nutrition of birds and swine. Antibiotics are also finding important applications in the treatment of various animal diseases caused by bacteria, spirochetes, and some of the larger viruses and in the treatment of certain plant diseases. It is, however, in the treatment of human diseases that antibiotics have made their greatest contribution. One may truthfully say that they have caused a revolution in medical practice. It is sufficient to review briefly the various infectious diseases, and to indicate how effective antibiotics have proven in controlling such diseases. Attention may also be directed to the need for new agents for the treatment of diseases that do not, at present, lend themselves to therapy.

1. *Diseases caused by cocci and various gram-positive rod-shaped bacteria.* Here belong infections caused by *streptococci*, *pneumococci*, *staphylococci*, *gonococci*, aerobic (anthrase) and anaerobic (tetanus) spore-forming bacilli, and various others. These bacteria are highly sensitive to penicillin and to a number of other antibiotics, notably aureomycin, chloramphenicol, and terramycin. Bacitracin and tyrothricin also have the capacity to attack in a highly efficient manner some of the infections caused by

these bacteria. Bacteria made resistant to penicillin, or strains naturally resistant to it, may be sensitive to some of the other antibiotics, notably, bacitracin or streptomycin. Combinations of two antibiotics, such as penicillin and streptomycin, are frequently more effective than a single agent.

2. *Diseases caused by gram-negative bacteria.* These bacteria are, for the most part resistant to penicillin and some of the other antibiotics. They are sensitive to streptomycin, chloramphenicol, aureomycin, neomycin, and terramycin, which have found extensive application in the treatment of infections caused by these bacteria. In some cases, as in whooping cough and typhoid, one antibiotic is preferable to others; in other cases, as in urinary tract infections, several substances may be effective, and can thus be used almost indiscriminately. Certain antibiotics are particularly effective in the treatment of a certain type of infection, as in the case of polymyxin for *Pseudomonas* infections. The possibility of utilizing the synergistic action of two substances, such as neomycin and bacitracin, or aureomycin and streptomycin, or of an antibiotic with a synthetic agent, such as streptomycin and sulfadiazine, offers considerable promise of exerting a greater effect and of overcoming the danger of potential development of resistance among the sensitive organisms. Synergistic action has proved particularly successful in the treatment of brucellosis and various other infections.

3. *Diseases caused by acid-fast bacteria.* Because of their peculiar characteristics, these diseases are among the most resistant to chemotherapy. The discovery that streptomycin can be utilized in the treatment of tuberculosis has provided a great stimulus in the search for new antibiotics as well as synthetic compounds that possess similar properties. This has given hope that the control of this highly important group of diseases is finally within our reach. The fact that streptomycin is not alone in this respect is indicated by the latent potentialities of a number of other antibiotics, notably, neomycin, viomycin, mycomycin, nisin, and viscosin. The possible development of strains of *M. tuberculosis* resistant to streptomycin suggested that supplementary use of other agents, such as para-aminosalicylic acid.

The treatment of leprosy has not been solved satisfactorily as yet, although some antibiotics have been found to be effective. Indications are, however, that sooner or later this ancient disease of man will be subject to satisfactory chemotherapy.

4. *Spirochetal diseases.* Several antibiotics, notably penicillin and bacitracin, have a remarkable effect upon syphilis and other diseases caused by spirochetes. The use of antibiotics in these infections has gradually superseded the methods of treatment current before the advent of antibiotic therapy.

5. *Rickettsial diseases.* These diseases, comprising typhus fever, scrub typhus, spotted fever, and a variety of others, are readily subject to therapy by a number of antibiotics. These include chloramphenicol, aureomycin, and terramycin, which appear to be able to control virtually this whole group of infections.

6. *Fungus diseases.* Various antibiotics are known to possess marked fungistatic and fungicidal properties. Unfortunately, they are all too toxic for general use. This is true of clavacin, streptothricin, actidione, fradicin, fungicidin, and many

others. Although none has as yet found application in the generalized treatment of fungus infections, sooner or later one or more will be found which will control some of these diseases.

7. *Protozoan and other diseases due to animal forms.* No true antibiotic is now known to be significantly effective against diseases caused by the malarial and certain other important protozoan organisms. The ability, however, of various antibiotics to affect amoebae, trypanosomes, trichomonads, and other protozoa has been definitely established. Some have already found practical application in chemotherapy. This is true, for example, of aureomycin, terramycin, and neomycin, which are used successfully against amoebic dysentery; it is claimed, however, that in some cases, at least, the effect consists largely in killing off the bacteria upon which the amoebae feed.

8. *Virus diseases.* Some of the larger viruses, notably the psittacosis and lymphogranuloma venereum groups, are susceptible to certain antibiotics, such as chloramphenicol, aureomycin, and terramycin. The usefulness of these antibiotics in other viral infections, such as trachoma, has been definitely established; other virus diseases, such as infectious mononucleosis, influenza, and so-called viral pneumonia, require further confirmation or elucidation. No antibiotic has so far found practical application in the treatment of the smaller viruses, of which the causative agents of the common cold and poliomyelitis are most important. Although there are reports of the formation by certain fungi and *Actinomycetes* of specific antiviral agents and although a polysaccharide of bacterial origin has been found to inhibit the multiplication of pneumonia virus in mice, the practical potentialities of these preparations have not been established.

9. *Neoplasms.* Tumor or cancer cells are known to be subject to the action of various microorganisms and their products. It is sufficient to mention the effect of certain bacteria such as *Sporosarcina ureae*, of trypanosomes such as *Trypanosoma cruzi*, and of fungi belonging to the *Aspergillus fumigatus*. The effective agents so far isolated have proved to be too toxic for practical use. The evidence so far obtained is suggestive, however, that sooner or later, suitable chemotherapeutic agents will be found.

10. *Plant diseases.* To complete the record of infectious diseases in relation to antibiotics, plant diseases due to microbial infections should also be included. Several antibiotics have been found to have the capacity of destroying various bacteria and fungi which are responsible for the causation of these diseases. This has aroused interest in the possibility of utilizing some of the antibiotics for practical control of such bacteria and fungi. Attempts have been made to use streptomycin in plant infections caused by gram-negative bacteria, actidione in various fungus infections, and certain other antibiotics in the treatment of legume seeds infected with fungi. The suppression of a number of plant parasites, especially root rots, by the plowing under of organic manures suggested the possibility that this action is due to the favorable development of antagonistic organisms which produce antibiotics.

In this survey, I have not touched upon the use of antibiotics in preoperative surgery, in the nutrition of nonruminant animals, in the preservation of biologic material, and in various other applications where their selective action upon different

groups of organisms can be utilized to great advantage.

I would like to dwell at somewhat greater length upon the role of antibiotics in the treatment of tuberculosis. The story of this disease is that of a continuous battle of mankind against one of its greatest enemies, one that had a particular capacity for attacking its victims at a time of great stress, as in postwar periods. No wonder that man has spoken of this dreadful disease as the "great white plague." Less than a decade ago, even after the introduction of the sulfa compounds and penicillin, the medical profession was inclined to the belief that no drug would ever be found which would be effective against tuberculosis. The discovery of streptomycin pointed a way to the successful chemotherapy of this disease. It has aroused hope that before very long this scourge of mankind will be brought under complete control. Although numerous antibiotics are now known to possess antituberculosis properties, as shown in Table I, streptomycin is still the only one that is extensively used, alone or combined with certain synthetic agents, in the treatment of tuberculosis.

TABLE I

Production of Antibiotics Possessing Tuberculostatic and Tuberculocidal Properties

Bacteria	*Actinomycetes*	*Lower fungi*	*Higher fungi*
Aytivin	Actinomycin	Aspergillic acid	Biformin
Bacillin	Aureomycin	Aspergillin	Clitocybin
Endosubtilisin	Antismegmatis factor	Citrinin	Grifolin
Esperin		Diploicin	Lactaroviolin
Eymycin	Litmocidin	Enniatin	Lateritiin
Gramicidin	Mycomycin	Gliotoxin	Nebularin
Licheniformin	Neomycin	Fumigacin	Polyporin
Micrococcin	Nocardin	Javanicin	
Nisin	Streptin	Mycocidin	
Pyolypic acid	Streptothricin	Usnic acid	
Subtilin	Streptomycin	Ustin	
Viscosin	Terramycin		
	Viomycin (Vinactin)		

Dr. H. C. Hinshaw, one of the leading authorities in the field and a pioneer in the use of streptomycin in tuberculosis, emphasized: "It has now become clearly evident that streptomycin is an agent which alleviates the symptoms of some of the most distressing types of tuberculosis, that it at least prolongs life in some of the most fatal types of tuberculosis infection and that it is a drug which must be used with great care and discrimination in many of the less serious and less fatal types of disease." Numerous other clinical investigators soon followed in emphasizing that streptomycin reversed the trend of tuberculosis, and the majority of the patients were improved. Streptomycin was found to bring about a rapid, sometimes abrupt, fall in temperature and accompanying symptomatic improvement, a regression, and frequently complete disappearance, of the pulmonary lesions demonstrable to x-ray. It was soon recommended that streptomycin be used in miliary tuberculosis, tuberculous meningitis, tuberculous sinuses and fistulas, and various forms of early and pulmonary tuberculosis.

The conclusion was reached that the most significant contribution of streptomycin was that it opened a way to the treatment of tuberculosis, that it has demonstrated

that the chemotherapy of this disease, like that of most other infectious diseases, is possible. It has stimulated a tremendous amount of research for new and better agents. In my recent travels through southern and western Europe, I was profoundly impressed by the successful results obtained in the treatment of certain forms of tuberculosis by streptomycin. As high as 75 per cent recovery was claimed for meningitis and miliary cases. Frequently, streptomycin was combined with other agents such as PAS or a sulfone, to avoid development of resistance. Its combined use with tuberculin has given some very striking results.

Tremendous progress has thus been made in recent years in the development of a new branch of chemotherapy, comprising the utilization of antibiotics, which is frequently referred to as "antibiotic therapy." As in any new field of science, however, certain important problems have arisen in connection with the use of antibiotics. The most significant of these is the development of bacterial resistance. This phenomenon has both a practical application and a theoretic significance which are closely related to our knowledge of the mode of action of antibiotics.

FUTURE OF ANTIBIOTICS

As one surveys the broader aspects of the subject of antibiotics; as one realizes that a mere fraction of the microorganisms present in the numerous soil types throughout the world, in various water basins, on numerous food products, and on many other substrates have so far been examined for their ability to produce antibiotics; as one visualizes the great variety of chemical compounds which are formed by these organisms and which have the capacity of inhibiting the growth of and even of destroying other microorganisms; as one finds that some of the isolated compounds are not very toxic to animals and possess properties which would render them desirable chemotherapeutic agents—one is inclined to become optimistic and hope that, before long, all human and animal infections, and possibly also plant infections, can be combatted if not completely eliminated by the utilization of antibiotics.

One may stop, therefore, and analyze the problems in the field of antibiotics that face us at present:

1. We recognize need for new antibiotics that are more potent than those known at present or are active against the infectious agents that have become resistant to known antibiotics. They should have a less undesirable effect upon the human and animal body or should possess more desirable physical, chemical, and biologic properties than the antibiotics now in use.

2. There is need for new antibiotics capable of exerting a synergistic action, when combined with other known chemical or biologic agents, in combating chronic diseases, such as brucellosis, leprosy, and tuberculosis.

3. There is need for antibiotics suitable for combating fungus diseases, filterable viruses, and neoplastic diseases.

4. There is need for a better understanding of the mode of action of antibiotics upon bacteria and other microorganisms on the mechanism of the development of resistance among sensitive organisms, and the problem of overcoming such resistance.

5. There is need for a better understanding of the role of antibiotics in animal nutrition and the over-all effect upon the human body when given parenterally, orally, or topically.

6. There is need for antibiotics to be used in the control of plant diseases.

7. There is need for a better understanding of the production of antibiotics in the soil and in other natural substrates which are inhabited by extensive populations of antibiotic-forming organisms and their effect upon plant growth. This may also help to elucidate the role of antibiotics in natural processes.

The search for new antibiotics will continue. New approaches will be found and new screening methods will be developed. Many new antibiotics will be found which will prove to be better than those now known, or which will act upon diseases not susceptible at the present time to chemotherapy. The problem of antiviral and antitumor agents will be investigated on a broader scale. Finally, better knowledge of the physiologic and biochemical mechanisms of the bacteria, viruses, and other pathogenic organisms affected by the various antibiotics may help to clarify the still obscure aspects of the mode of action of antibiotics, and thus possibly lead to the discovery or even to the synthesis of new and better chemotherapeutic agents. The prospects for antibiotics are promising; the future is bright indeed.

Autopsies

MEDICO-LEGAL IMPORTANCE

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A proper post-mortem examination may involve many medico-legal and pathologic problems with variations. These examinations may be required not only after death, but also long after putrefaction had set in.

An autopsy is a thorough viewing of the body including an opening of same with an examination of all organs. Microscopic, chemical, and biologic examinations of all the contents should be done in order to ascertain the cause of death. All diseases or abnormalities should be carefully noted by the pathologist so that conclusions as to the cause of death may be ascertained. After a body has been buried, the court may order a disinterment for several purposes, such as identification, cause of death, poisoning, etc.

Any unauthorized interference with a corpse will give rise to a cause of action by the nearest relatives of the deceased. (*Stahl v. Wm. Nicher, Inc.* 184 *App. Div.* 85, 171 *N.Y.S.* 728.) However, where a physician performs an autopsy under the direction of legal authorities and with ordinary care and skill, he will not be liable to the relatives of deceased even though they have not given their consent. (*Cook v. Walley* 1 *Colo. App.* 163, 27 *Pac.* 950.)

An insurance company's right to a medical examination of the body of the insured after injury or death is often provided for in insurance policies. Courts have held generally that this is a valid and enforceable provision of the contract. (*Standard Acc. Ins. Co. v. Rossi* 35 *F 2d* 667.) Furthermore, courts have held that the granting of permission for an autopsy is a condition precedent to establishing a claim for double indemnity. (*Dvorkin v. Commercial Travelers* 17 *N.Y.S. 2d.* 109.)

However, it is important to remember that the insurance company's request or permission for an autopsy must be obtained by the coroner or medical examiner. Statutes in various states protect medical examiners in performing autopsies. The request for autopsy by an insurance company must be made within a reasonable time, otherwise the company will be deemed to have waived its right under the contract. What constitutes a reasonable time depends upon the facts and circumstances of the case and one very important consideration is whether or not the body has been interred. (*Ewing v. Comm. Travelers* 55 *AD* 241, 66 *N.Y.S.* 1056.) However, such rights are usually exercised a reasonable time before interment. (*Wehle v. U. S. Acc. Assn.* 153 *N.Y.* 116.) Provisions in accident policies for autopsies after burial are void. (*U. S. Fid. & Gar. Co. v. Hood* 124 *Miss.* 584.) Furthermore, negligent performance of an autopsy makes the insurer liable. (*Thompkins v. Pac. Mutual Life* 53 *W. Va.*, 479.)

Decided cases generally treat the unauthorized dissection as an interference with a legal right. The legal right is the right to have immediate possession of the body in its condition at the time of death and control for burial.

Courts claim that there is no property in a corpse. (*Finley v. Atl. Trans. Co.* 220 *N. Y.* 249.) The right to possess, preserve and bury it, however, belongs, in the absence of testamentary direction, to the surviving spouse, if there is one, and if not, to the next of kin who may maintain an action thereon for deprivation or mutilation. (*Hasselbach v. Mt. Sinai Hospital* 173 *AD* 89, 159 *N.Y.S.* 367.)

A mother, when she is the nearest surviving relative and next of kin, is entitled to the disposition of the dead body of her son. (*Darcy v. Presbyterian Hosp.* 130 *AD* 496, 114 *N.Y.S.* 1052.) Where there is no surviving spouse, the children (as next of kin) share equally, and it is necessary to secure the permission of all the children to perform an autopsy.

We may therefore summarize by stating that *proper permission* to perform an autopsy is of paramount importance, because the failure to do so leaves the coroner, medical examiner, pathologist, and insurance company liable for damages. (*Hassard* v. *Leband* 143 *AD* 424-128 *N.Y.S.* 161.) Although this permission for an autopsy need not be in writing, it is always a safeguard that protects all to secure this permission not alone for an autopsy but to have the body disinterred if necessary. In some jurisdictions, the consent of the health authorities must also be obtained. Under section 42-b of the Sanitary Code of New York City, a court order is now required in any case where a body has to be disinterred.

One must not feel, however, that the mere permission or court order protects the medical examiner, coroner, pathologist, or funeral home from suits arising out of damages. All autopsies should be performed in a proper establishment screened from public view. Many suits for damages for "mental anguish" have been brought because the remains were exposed to public view.

In a recent Kentucky case, a worker fell from a ladder and died in a short time. The insurance carrier requested the coroner to order an immediate autopsy in order to rule out accidental death. Without obtaining consent of the widow, the coroner directed an autopsy to be performed. Two physicians, observers for the insurance company, witnessed the autopsy.

The widow brought an action to recover damages for the unlawful mutilation or dissection of her husband's body. She named as defendants the coroner, the insurance company, the pathologist who performed the autopsy, and the two physician-observers, all whom she alleged had conspired to perform an autopsy without her consent.

The trial court found for all defendants except the coroner. On appeal, the court ordered a new trial insofar as verdicts against the insurance company and pathologist as well as the coroner were in order.

The Court of Appeals stated that a physician who performs an autopsy at the request of the coroner is not liable in damages if the order of the coroner was authorized and valid. If, however, the coroner exceeds his authority, his order or request affords no protection to a physician who performs an illegal autopsy.

In the above case, the insurance company had a motive for obtaining an autopsy. If it could be proven that the patient died of a heart condition or disease, the insurance company would be relieved of any liability. However, it is obvious that per-

mission from the widow should have been obtained. The Kentucky statutes — section 528 — provides: "It shall be the duty of the coroner, upon request, or when he has reason to believe a crime has been committed, to hold an inquest upon the body of any person slain, drowned or otherwise suddenly killed."

When a lawful inquest is being held and a post-mortem examination is deemed necessary, within the limits and under the circumstances stated, the coroner may cause an autopsy to be performed. A coroner has no lawful right, however, to conduct an inquest or to cause an autopsy to be performed, unless he has reason to believe that a crime has been committed or has been requested to do so by one who is authorized to make such a request. The right of a surviving spouse or of the next of kin in the body of the deceased cannot be subordinated to anything less than overriding public interest sanctioned by law.

Since the autopsy was wholly unauthorized and illegal, the coroner and all persons who assisted, advised, commanded, or cooperated in conducting it are liable to plaintiff for damages. (*Streipe v. Liberty Mutual Ins. Co.* 47 *S. W.* (*2nd*) 1004.)

In an Oklahoma case, an insured died of sunstroke. His insurance company promised to pay benefits under a policy insuring "against the effects resulting directly and exclusively of all other causes, from bodily injuries sustained solely through external, violent and accidental means." The company in this case contended that insofar as death was not accidental, it was not liable on the policy. Verdicts for plaintiff were sustained in Trial and Supreme Courts.

In this case, the Supreme Court stated that "accidental means" is to denote "accidental cause" and in the case of sunstroke, if the same was suffered while the insured was engaged in his usual avocation or going about his affairs in an ordinary manner, as any other person might have been under like or similar circumstances, and did not intentionally or voluntarily subject himself to an intense heat calculated to produce sunstroke, with the knowledge that it would probably occur, then the sunstroke was suffered from "accidental means" or "accidental cause" within the meaning of the policy.

The insurance company further contended that it was denied the right to have an autopsy made. The request from the company was made nine days after the insured was buried.

The court contended that no claim was made that an autopsy would have disclosed that the insured died of or from any cause other than sunstroke. Furthermore, the beneficiary never refused an autopsy within the terms of the policy, nor was an explanation clear as to the delay by the company in requesting the autopsy. (*Provident Life & Acc. Co. v. Green* (*Okla.*) 46 *P.* (*2d*) 372.)

In *Grauunder v. Beth Israel Hospital* (*N. Y.* 272 *N. Y. S.* 171), the plaintiff's husband died in defendant's hospital at 8 p.m. The latter had an autopsy performed without consent of the widow. The plaintiff sued the hospital, and the judgment in her favor was upheld in Trial and Supreme Court.

The court stated that the defendant hospital owed a duty to plaintiff to protect her husband's body while in possession of hospital against any post-morten examinations without her written permission.

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Treatment of Hemorrhagic Disorders in Infants and Children*

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NEW YORK, N. Y.

Hemorrhage is an alarming symptom. It can be arrested temporarily by empirical procedures. But the only rational approach beyond emergency measures is based on an individual study of the clotting mechanism and vascular endothelium. The tests on which such diagnosis depends are relatively simple. They must supplement a careful history and physical examination to determine the precise deficiency responsible for abnormal bleeding.

EMERGENCY TREATMENT OF ACUTE HEMORRHAGE

Arrest bleeding: When a patient is first seen, the underlying reason for an acute hemorrhage may not be apparent. No matter what the cause, be it traumatic or otherwise, tourniquets can be applied to extremities, pressure to other areas, gauze packed into accessible cavities, bleeding points ligated, or ice applied if internal bleeding is suspected. To oozing surfaces, thrombin solution, fibrin foam, or an oxidized cellulose or gelatin sponge, and pressure should be applied. Fluid by mouth should be administered provided that bleeding is not from a cerebral injury or perforating wound of the gut.

Restore blood volume: Restore blood volume by slow, continuous, intravenous drip of protein fluids, i.e., blood, plasma or serum. Saline or crystalloidal solutions rapidly leave the circulation and thus restore blood volume only temporarily. In the absence of extensive tissue damage, blood pressure should rise approximately 1 mm. Hg. for each ounce of protein fluid infused. The addition of ascorbic acid to intravenous fluids will increase oxygen availability and tend to prevent irreversible tissue injury from anoxemia.

Complete the diagnosis: In order that further treatment be rational, one must first determine the etiology. A careful history may reveal some disorder of which bleeding may be a symptom. The family history may arouse suspicion of hemorrhagic

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disease. Physical examination may turn up a diagnostic clue from the site of the hemorrhage or may reveal telltale evidence of purpura following simple percussion. Simple tests will determine whether the deficiency is in the vascular system or in the clotting mechanism, or in both.

HEMORRHAGIC DISEASE OF THE NEWBORN

Prevention involves oral or parenteral administration of 5 mg. vitamin K to the mother for several days before delivery. Such prophylactic treatment is particularly indicated in maternal toxemia or in premature or difficult labor in order to prevent intracranial hemorrhage. Treatment involves intra-muscular injection of 1 mg. of vitamin K every 6 hours until bleeding ceases. Hemorrhage may be arrested more rapidly by injection of 8 cc. fresh whole blood per pound of body weight of the same type and Rh factor, if the newborn is female. The baby should be fed by bottle or dropper rather than by the breast.

HEMOPHILIA

Mild hemorrhages may be controlled by compression with natural hemostatics, such as fresh human serum, freshly cut meat, and placental, lung, or brain extract, or with artificial preparations, such as thromboplastin solution, hemostatic globulin, or fibrin foam saturated with epinephrine or thrombin solution. Whatever the agent, it should be cold to contract the affected blood vessels.

Severe hemorrhages may be controlled by repeated transfusions of 100-200 cc. whole blood (fresh or stored) or fractionated human plasma (fresh, frozen, or dried) every 8 hours. Loose clots adherent to the bleeding site should be removed with saline solution and the edges approximated without sutures. Thrombin prepared from human blood is then applied directly to the site of bleeding on dressings and kept in place for days.

Plasma is preferable to whole blood, because it contains twice the amount of thromboplastinogen present in whole blood. Since the level of this clotting factor must be raised in hemophilia in order to arrest bleeding, large volumes of plasma must be injected at a time. The greatest danger in hemophilia is pressure of hematomas upon vital structures. Pressure symptoms must be relieved by aspiration or drainage after administration of 250 cc. fresh or lyophilized plasma.

Repeated transfusions may make the child refractory to blood because of the development of antibodies. He may respond to totoluidine blue or protamine sulfate therapy. Both neutralize heparin following intravenous administration by continuous slow drip. The initial dose is about 5 mg. per kilo body weight dissolved in 300 to 500 cc. saline solution. Daily injections may be given without untoward effects.

Histamine therapy produces greater disintegration of stable platelets in the circulation. I encountered no reaction to histamine therapy in the mild hemorrhages. There is no substitute for blood transfusion in severe bleeding.

THROMBOCYTOPENIA

Minor hemorrhages may be arrested by local application of thromboplastin, placental coagulant, rabbit globulin, or snake venom; by subcutaneous injection of moccasin venom to improve capillary resistance; by intramuscular injection of parathyroid extract to induce hypercalcemia. The most effective method of checking hemorrhage and relieving anemia is blood transfusion. The platelet count may be but little improved by this, but the bleeding time is brought under control. Drugs, allergens, or infections must be eliminated.

Table I presents the differential diagnosis of hemorrhagic disorders of infants and children. The first column gives the five deficiencies responsible for bleeding; four are in the clotting mechanism and one in the vascular endothelium. The second column presents the tests essential for establishing the diagnosis and the results to be expected from the deficiency. The third column reveals the disease entities produced by the deficiency. The history and physical examination point to specific hemorrhagic disorder.

Major hemorrhages respond to repeated small transfusions of fresh blood given at intervals ranging from one to several days depending on the response. In my experience, fresh blood with normally dispersed platelets produces a more dependable response than stored blood. Platelets agglutinate within a few hours in stored blood. Once the anemia is corrected by repeated transfusions, freshly centrifuged blood plasma, which is rich in platelets, should be injected. This must be given promptly, before platelet agglutination diminishes its effectiveness.

Recurrent hemorrhages, persisting after repeated transfusions, respond to splenectomy, which should be carried out during the quiescent stage of the disease when the operative mortality is about 5 per cent. After operation, bleeding ceases immediately and platelets rise to high levels for a week or two before falling to normal or low levels. The bleeding time is more favorably affected than the number of platelets or the retractility of the clot; therefore, one must infer that splenectomy improves capillary resistance. A careful search for accessory splenic tissue, liver, and mesentery lymph nodes must be made for immediate histologic study. Since as little as 5 Gm. of splenic tissue may precipitate a relapse, it is necessary to locate aberrant splenic tissue by thorotrast visualization. When hyperfunctioning reticuloendothelial phagocytes are present in the liver and lymph nodes, serial blood transfusions will be necessary after splenectomy.

Splenectomy is contraindicated if the blood picture suggests aplasia with severe anemia and neutropenia or if marrow shows diminished platelets and/or megakaryocytes. The chances for continued recovery are about 30 per cent following medical treatment and 70 per cent following successful splenectomy. Death may occur from severe external hemorrhage, bleeding into vital tissues, marked anemia, or extreme exhaustion.

SYMPTOMATIC THROMBOCYTOPENIA

Purpuric manifestations may develop at the onset of such acute infections as pneumonia, exanthemata, meningococcal toxemia, septicemia, subacute bacterial

TABLE 1

Differential Diagnosis of Hemorrhagic Disorders of Infants and Children

	Test	*Disease*
Prothrombin Deficiency	Prothrombin Time: Prolonged Clotting Time: Prolonged Clot Retraction: Poor Bleeding Time: Normal Platelet Count: Normal	Congenital Hypoprothrombinemia Hemorrhagic Disease of Newborn Congenital Obstruction—Bile Ducts Idiopathic Congenital Hypoprothrombinemia Acquired Hypoprothrombinemia Digestive Disorders Liver Disorders Chemical Poisoning—Dicumarol Chemical Poisoning—Salicylates
Thromboplastinogen Deficiency	Clotting Time: Prolonged Bleeding Time: Normal Platelet Count: Normal Clot Retraction: Normal Family History: Bleeding Joint Effusion Male Patient	Hemophilia
Platelet Deficiency	Bleeding Time: Prolonged Platelets: Decreased Clot Retraction: Poor Capillary Fragility: Increased	Primary Thrombocytopenic Purpura Symptomatic Thrombocytopenic Purpura
Fibrinogen Deficiency	Clotting Time: Prolonged Bleeding Time: Prolonged Platelet Count: Normal	Congenital Afibrinogenemia Congenital Hypofibrinogenemia Acquired Hypofibrinogenemia
Vascular Deficiency	Capillary Fragility: Increased Capillary Microscopy: Abnormal Bleeding Time: Prolonged Blood Clotting Tests: Normal	Hereditary Vascular Purpuras Hereditary Telangiectasia Hereditary Thrombasthenia Constitutional Thrombopathy Acquired Vascular Purpuras Scurvy Purpura Simplex Henoch's Purpura Schoenlein's Purpura Infectious Purpura Purpura Fulminans Waterhouse-Friderichsen's Syndrome Mechanical Purpura

endocarditis, typhus, and others. The striking fall in platelets is usually accompanied by increased vascular permeability. Thrombocytopenia often occurs during convalescence from measles. In allergic disorders thrombocytopenia may accompany any type of sensitivity. Purpura may follow readministration of drugs such as arsenobenzine, sulfonamide, quinine, phenobarbital, Sedormid, gold salts, bismuth, and iodine. Purpura may also follow ingestion of food allergens, inhalation of orris root; injection of animal allergens, such as snake venom and vaccines; or insect bites and burns.

In aplastic anemia all parts of the bone marrow are involved. Erythropoietic tissue is primarily affected and megakaryocytes secondarily—hence the reduction in platelets. In leukemia the bone marrow is displaced with leukoblastic tissues.

Marrow metabolism becomes too defective for megakaryocytes to proliferate. Chemical poisoning produced by such substances as arsenic and benzol and the toxins produced by burns greatly affect bone-marrow metabolism. The proper number of platelets can no longer be formed from the megakaryocytes.

Some chemical poisons may also injure capillary endothelium and thus increase the extent of the bleeding. In irradiation therapy with x-ray, radium, and radioactive sodium, the bone marrow may be injured with consequent reduction in platelets. In Banti's disease, Felty's syndrome and Gaucher's disease, the spleen becomes overactive, causing increased destruction of platelets. This pathologic activity of the spleen, or hypersplenism, is accompanied by an increase in mature megakaryocytes, normal platelet formation, but increased platelet destruction.

HEREDITARY THROMBASTHENIA

This rare familial bleeding tendency is transmitted by both sexes. It is characterized by excessive bleeding, easy bruising, and purpura. Bleeding time is prolonged, clot retraction is poor, but clotting time is normal. This disease is attributed to defective function of the platelets despite their normal numbers. Although the condition resembles thrombocytopenic purpura, treatment is symptomatic.

CONGENITAL HYPOFIBRINOGENEMIA

Hemorrhages can be controlled by giving transfusions of whole blood or fresh plasma. More effective therapy involves intravenous injection of Cohn plasma fraction I, which provides 60 per cent fibrinogen. Administration of 200 mg. at the onset of bleeding will maintain blood fibrinogen at the normal level of 200 mg. per cent. Since the child's blood level of replaced fibrinogen gradually diminishes within 30 days to about 50 mg. per cent, the critical level for bleeding, the same dose of plasma fraction I should be injected at monthly intervals. Pure fibrinogen solution is a life-saving measure in preventing fatal hemorrhage from hypofibrinogenemia once the condition is recognized.

ACQUIRED HYPOFIBRINOGENEMIA

Symptomatic hypofibrinogenemia occurs in deficiency diseases, e.g., scurvy, pellagra, and pernicious anemia; in bone marrow disease, especially myelogenous leukemia and polycythemia; in liver diseases where extensive injury reduces fibrinogen formation; and, of course, in severe infectious diseases such as scarlet fever, pneumonia, tuberculosis, and brucellosis, which destroy liver structure and increase circulating fibrinolysin.

HEREDITARY TELANGIECTASIA

Nosebleeds may be arrested by tampons of styptics, thrombin, or fibrin foam. Cauterization of the bleeding points with a chromic acid bead, electrocoagulation, or submucous injection of 5 per cent quinine and urethane may be effective. Vitamin P or 50 mg. rutin with 250 mg. ascorbic acid three times a day decrease capillary permeability. Ferrous sulfate gr. V three times a day corrects the hypochromic

anemia when present. When surgery is contemplated, no special procedures to prevent bleeding are required because the blood clotting components are normal.

CONSTITUTIONAL THROMBOPATHY

This rare hereditary disease is transmitted by both sexes to males and females. It is characterized by prolonged bleeding time with defective capillaries. The clotting time is normal, clot retraction efficient, and platelet count adequate. Treatment is symptomatic.

PURPURA SIMPLEX

An hereditary disorder in allergic families produces symmetrical purpuric spots about the hair follicles and limbs following an attack of headache, fever, and malaise. If severe, the bleeding may be intramuscular, subperiosteal or visceral, accompanied by allergic skin lesions.

SCURVY

Infants develop swollen, bleeding gums and painful subperiosteal hemorrhages. Hematuria is the earliest sign of infantile scurvy. Hemorrhage into the orbital fossa with "black eye" is rare. Hemorrhage into the skin, common in adult scurvy, is rare in infants. Cerebral hemorrhage may be found at postmortem. All clotting tests are normal, but capillary fragility is markedly increased. Hemorrhagic symptoms clear promptly with administration of 60 mg. ascorbic acid or 4 oz. orange juice daily.

HENOCH'S PURPURA

An allergic gastrointestinal disturbance is produced by an urticarial serohemorrhagic effusion into the intestinal wall. There may be ecchymoses, hematemesis, melena or hematuria accompanied by abdominal or renal colic. An attack begins with vomiting, fever, diarrhea, abdominal distention, and colic before any purpuric eruptions develop. The clinical picture may simulate an acute abdominal emergency. The urine may contain red cells and albumin as in glomerulonephritis.

SCHOENLEIN'S PURPURA

A joint affection of adolescents is a migratory disturbance produced by periarticular effusions. The affected joints become purpuric, painful, swollen, tender, hot, and red. However, hemorrhage into the joints never occurs. Fever, malaise, and indigestion clear with antihistaminics.

INFECTIOUS PURPURA

Capillary injury by toxins produces purpura in scarlet fever, measles, pneumonia, diphtheria, acute glomerular nephritis, typhus, smallpox, spotted fever, meningococcic meningitis. An initial reduction in the platelet count is gradually overcome in the later stages of the infection. Purpuric manifestations may also be produced by bacterial emboli as in subacute bacterial endocarditis, typhoid fever, and meningococcic septicemia. Organisms can often be demonstrated in such purpuric skin lesions.

PURPURA FULMINANS

Large symmetrical ecchymoses appear over the skin surfaces. In such cases, bleeding never occurs from mucous membranes or from internal viscera. The blood platelets are normal, but capillary resistance is diminished. The centers of vascular innervation in the spinal cord are involved. The child usually succumbs within four days. Daily intravenous infusions of the amino acid methionine, 3 Gm. in 500 cc. saline, have relieved such purpura in patients suffering from scarlet fever.

WATERHOUSE-FRIDERICHSEN SYNDROME

Bilateral hemorrhage into the adrenal glands produces cyanosis, shock, and fever. Respirations become rapid and labored, and the child sinks into a deep coma. Petechial and purpuric spots appear over the entire body and coalesce into ecchymoses. In the newborn the adrenal hemorrhage is induced by birth trauma. In the infant and older child, the condition is precipitated by infection—meningococcic, streptococcic, pneumococcic, or diphtheritic. Treatment of this desperate condition must be immediate. Sulfas and antibiotics will combat the infection. Intravenous infusions of plasma, dextrose, and saline should be reinforced with 10 to 30 cc. adrenocortical extract daily. Vitamin K is added for the newborn and vitamin C for the older child. The course is rapidly fatal unless the patient is treated intensively from the onset.

MECHANICAL PURPURA

Capillary bleeding may be induced in a normal child in any region of the body subjected to sudden increase in venous pressure. Whooping cough may produce bleeding from the conjunctivae, nose, eyelids, and bronchi. Rheumatic heart disease may cause epistaxis or petechial hemorrhages in the extremities. Convulsions may produce purpura in the head and upper extremities from increased pressure within the blood vessels. Uremia may cause cerebral, retinal, and intestinal hemorrhage from the concurrent hypertension. Leukemia may cause bleeding by infiltration of the walls of the blood vessels. Exposure to extremes of heat or cold may cause the affected area to bleed. Chronic anoxemia of a part of the body may lead to localized petechial hemorrhage. Trauma may induce vascular purpura in the affected region. Prolonged standing may cause orthostatic purpura in the lower extremities if the capillaries are defective.

Any type of *vascular purpura* will respond to vitamin C and 100 mg. of vitamin P (hesperidin or rutin). Capillary permeability may further be decreased by parenteral injection of 10 per cent calcium gluconate (5 to 10 cc.) three times a day. Allergic purpuras respond to antihistaminics. Histamine diphosphate may be injected as a desensitizing agent, beginning with 0.1 mg. subcutaneously, gradually increasing at two to seven day intervals to 1 mg. In severe cases, 2 mg. histamine may be added to parenteral fluids. A maintenance dose of 1 mg. weekly is continued while skin tests determine the causative allergens.

ACKNOWLEDGMENT

We are indebted to *Ciba Clinical Symposia* for textual material written by Dr. I. Newton Kugelmass and appearing in the April *Symposia*, which is used in "Treatment of Hemorrhagic Disorders in Infants and Children." Tables and summaries for this same article were taken from Kugelmass' "Blood Disorders in Children", Oxford University Press.

GENERAL PRACTICE CLINICS

VOL. 10 NO. 2 FEBRUARY 1953

3. *Overnutrition and Obesity.* H. H. MITCHELL, Urbana, Ill. J. Clin. Nutrition *1*:66–76, September-October, 1952.

The storage of all essential nutrients in the body may be "vital" or "reducible" in character, depending upon the essentiality of such stores to the continuance of life. The "reducible" stores are the result of overnutrition in the sense that they represent consumption in excess of current requirements. The reducible stores are mobilized to meet emergency demands for nutriment beyond the capacity of the current food supply; in moderate amounts they are useful insurance, and under favorable nutritional conditions are provided by the diet. Moderate overnutrition with proteins, minerals, and vitamins is rarely a hazard to health.

Stores of fat may also be separated into "vital" and "reducible" portions, but unlike the other nutrients, the reducible portion can be increased to such an extent as to impair health and probably to shorten the normal life span. Hereditary factors, determining the somatotype of the individual, seem to dominate the inception of obesity. Endomorphy in particular involves apparently an inefficient homeostatic mechanism for the maintenance of body weight, permitting a complete breakdown of homeostasis if dietary habits are not kept under constant surveillance. Of course, other factors are also involved.

The evidence for the involvement of obesity in the etiology of a variety of diseases affecting later life and many organ systems seems to be incomplete in so far as a direct causal relation of obesity to disease is assumed, on the basis merely of a greater incidence of these diseases among obese than among nonobese persons. Whether weight reduction is effective in avoiding these degenerative diseases, or in curing or alleviating them when present, is problematical. The disadvantages of excessive overweight, however, cannot be doubted. Emphasis should be placed on restricted consumption of fatty foods in particular for many reasons which are discussed in the text. —*Author's abstract.*

4. *Alcoholism as a Nutritional Problem.* ROGER J. WILLIAMS, Austin, Texas. J. Clin. Nutrition *1*:32–36, September-October, 1952.

A nutritional deficiency is suggested as a basis of alcoholism. The author bases his thesis on three lines of evidence: (1) recent discoveries in the field of biochemical genetics which demonstrate the individuation of the metabolic mechanism and hence of nutritional requirements; (2) direct experimentation in animals; (3) clinical data.

Experiments with a colony of rats showed: (1) that the response to alcohol of animals on a basic diet differed markedly between individuals; (2) that those fed a marginal diet (deficient especially in B vitamins) drank excessively; (3) that those offered an abundant diet—rich in all the nutrients essential to the rat—drank only moderately; and (4) that those which had drunk excessively during the deficient regimen *stopped drinking* when they were given the nutrients they had lacked. It is concluded that on the basic diet the individual variations in the response to alcohol were determined by individual metabolic differences; that on the marginal diet the appearance of deficiencies provoked a desire for alcohol in all the animals; that with the abundant diet no deficiency developed and therefore no excessive desire for alcohol.

The applicability of these data to man is examined. Several individual cases are reported which seem to confirm them, and a large-scale experiment now in progress (Harvard School of Public Health) is mentioned, the preliminary results of which indicate that nutritional supplements cause a decrease in the quantity of alcohol consumed by man.

The author does not wish to exclude psychologic and social factors from the picture of alcoholism, but he believes that the nutritional factor, whether primary or secondary, gives an important key to a better understanding of this grave problem.

5. *Effects in Rheumatoid Arthritis of Hydrocortisone and Cortisone Injected Intra-Articularly.* MORRIS ZIFF, EDWARD SCULL, DENYS FORD, CURRIER MCEWEN, AND JOSEPH J. BUNIM, New York. Arch. Int. Med. *90*:774–84, December, 1952.

Nine patients with rheumatoid arthritis and one with rheumatoid spondylitis received intra-articular therapy with hydrocortisone. Seven of these had bilateral effusions in the knee joints permitting comparison of the effects of intra-articular injections of hydrocortisone, cortisone, and suspending vehicle in the same patient. Eighty per cent of injections with hydrocortisone (25 mg.) were followed by 2+ objective improvement or better when the patient was examined 3 days later; 95 per cent of injections were followed by significant improvement in the properties of the synovial fluid. Only 31 per cent of injections with cortisone (25 mg.) were followed by similar improvement clinically, and 23 per cent in the properties of the synovial fluid. There were no instances of 2+ objective improvement after injection of suspending vehicle, and only 14 per cent of injections were followed by significant improvement in the synovial fluid. Prolonged periods of improvement were induced in three patients following intra-articular injection of hydrocortisone lasting from 27 to 90 days; the average duration of improvement in the others was 8 days and varied from 4 to 15 days. The most consistent changes in the synovial fluid after intra-articular hydrocortisone were a rise in viscosity and a fall in aminotripeptidase content. These changes were accompanied by fall in the leukocyte count and an increase in the per cent of lymphocytes. Total protein and albumin-globulin ratios were not consistently altered. The aminotripeptidase

content of the synovial fluid appeared to be a useful index of the degree of synovial inflammation. Marked increase in relative viscosity of the synovial fluid was associated with a relatively small change in glucosamine concentration, suggesting that the rise in viscosity following intra-articular hydrocortisone is due to an increase in the state of polymerization of synovial hyaluronate. Intra-articular therapy found continued utility in the treatment of 4 out of 10 patients. The therapeutic usefulness of this procedure on a long term basis remains to be evaluated. 14 references. 2 figures. 4 tables.—*Author's abstract.*

6. *Dietary Treatment of Hypertension.* IRVINE H. PAGE AND A. C. CORCORAN, Cleveland, Ohio. J. Clin. Nutrition *1*:7–16, September-October, 1952.

In spite of the belated application of scientific method to the study of low sodium dietotherapy in hypertension, it has now been shown that a minority of patients with established essential hypertension respond favorably to diets containing about 0.2 Gm. sodium in each day's intake. In such diets, protein intake may be sustained by use of sodium-poor milk powder or similar preparations, or it may be sacrificed as in the rice diet. The choice is determined by the needs and possibilities of the patient.

Psychologic, social and economic, as well as functional factors powerfully influence the success or applicability of low sodium dietotherapy. Lacking other proven means of speedy selection, the "proof of the pudding is in the eating" of a low sodium diet for at least 6 weeks, during which time the adequacy of sodium restriction is ensured by frequent checks of urinary sodium output. The cation-exchange resins are not as yet adequate substitutes for a rigid sodium restriction in the treatment of hypertension.

The combination of low sodium dietotherapy with other modes of treatment is generally deprecated unless it can be shown that the combined treatments have advantageously additive or synergistic effects. To date, the most definitely advantageous combination is the special case of combined hexamethonium, low sodium dietotherapy.—*Author's abstract.*

7. *Puncture of Goiters for Aspiration Biopsy.* NILS SODERSTROM, Sweden. Acta med. Scandinav. *144*:237–44, October 12, 1952.

A method is described for performing diagnostic puncture of goiters. The gland is punctured with a fine needle, some fluid material is aspirated and smears from this material are stained using routine hematologic methods. The method has been used in 100 cases, in 77 of which satisfactory smears were obtained.

Several types of thyroid cells occurring in the smears are described. An attempt is made to evaluate the diagnostic significance of some of these cell types. A certain type of large, granulated cells seem to be typical of non-toxic colloid goiters. Cells with another characteristic type of granulation —paravacuolar granules— possibly indicate the presence of hyperfunctioning thyroid tissue. 6 references. 9 figures. 1 table.

book reviews

Abundant Life, A Doctor Speaks of Health. FRANCIS H. GLAZEBROOK, M.D. Boston, The Christopher Publishing House, 1952.

Every intelligent person should be interested in the basic principles of physical growth and development and the ordinary means of keeping well. Health is greatly a matter of what you make it, and the way you live today determines your health of tomorrow, says the author, and he has endeavored throughout his book to give the answers to many of the questions people have asked him regarding the cause of various health disorders. He claims practicing physicians do not have the time or opportunity to educate the masses about routine living, and for this reason he has tried to present some essential facts about health and living. He hopes his book will be of interest and arouse in the readers the will to establish a reasonable routine of living, which should help to keep their bodies well and result in a comfortable long life.

In the main, the author has avoided recommendations for treatment and also specific diets. These he feels are up to one's personal doctor. Too much emphasis cannot be placed on the importance of diet and nutrition is Dr. Glazebrook's belief, which is based on fifty years of experience concerning pediatrics, surgery, obstetrics and medical diagnosis. Optimal nutrition is the first answer to good health and longevity. Man lives on what goes into the blood, and health, in fact life, is what the blood is.—*I. Newton Kugelmass, M.D.*

Applied Physiology. SAMSON WRIGHT, New York, Oxford University Press. Price $9.00.

This edition is virtually a new book reflecting the present state of diversified knowledge. But the opening chapter on the regulation of the internal environment still goes back to the classical theme of Claude Bernard. The constancy of the internal environment is still the generalization of physiology. The author has illustrated the principle with many examples taken out of conventional classification. On the clinical side this chapter deals with such practical topics as water and salt, lack and excess; renal function and failure; acidemia and alkalemia, diabetes insipidus; edema and disorders of the spinal fluid. All other phases of physiology are presented clearly and precisely. The manual elucidates how the various functions of the body are performed. Throughout emphasis is laid on those functions which are commonly deranged in disease. The beauty of the text is the sense of coordination and integration it gives to the organs and systems of the body—for example, in considering the cerebellum a full account is given of symptoms and signs of lesions in this structure in the human subject. This enables the student to draw his conclusions concerning the functioning of the organ and at the same time familiarize him with different aspects of the disorders of the cerebellum. This condensed textbook exemplifies the clearest presentation of a complicated subject of any of the texts now extant.—*I. Newton Kugelmass, M.D.*

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INTRODUCTION

The FIRST INTERNATIONAL CONGRESS OF BRONCHOESOPHAGOLOGY was held in Rio de Janeiro, August 28 and 29, 1952, in conjunction with the Second International Congress on Diseases of the Chest. Over twenty papers were presented by speakers from six different countries.

The International Bronchoesophagological Society has been fortunate in making arrangements with the Washington Institute of Medicine for publishing the Transactions of this First Congress, and the first group of papers were published in the December issue of the QUARTERLY REVIEW OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY. Another paper appears on the following pages of this issue.

The Second International Congress of Bronchoesophagology will take place in Belgium in June of 1953, under the presidency of Professor Fernand Eeman of Ghent. The Society now numbers over two hundred members, representing over 30 different countries. Anyone interested in becoming a member of this Society should communicate with the Executive Secretary-Treasurer, Chevalier L. Jackson, 1901 Walnut Street, Philadelphia 3, Pa. —CHEVALIER L. JACKSON

FOREWORD

The objective of the QUARTERLY REVIEW OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY, now incorporated in the INTERNATIONAL RECORD OF MEDICINE, is to bring together in one publication, in concise form, the essence of all that is published in otology, rhinology, laryngology, bronchology and esophagology from the world's voluminous literature, so that with a minimum of time and expense you are enabled to keep abreast of the rapid progress in these special fields of medicine and surgery.

The organization and simplification of the new data and the separation of the less significant findings from the important facts keep you continuously posted. The QUARTERLY REVIEW OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY brings you many new clinical discoveries—improved technics—world-wide research—a vast fund of important data, all in concise form.

The clinical facts presented here are systematically gathered from every available source. They are condensed from more than 300 medical and surgical periodicals, transactions and special publications and are properly classified and indexed for quick reference.

A section entitled "The International Record of Otorhinolaryngology and Bronchoesophagology" is included and consists of advanced experimental and clinical reports in otorhinolaryngology and bronchoesophagology.

Quarterly Review of OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY

VOLUME 12 NO. 1 **FEBRUARY 1953**

Incorporating the International Record of Otorhinolaryngology and Bronchoesophagology

Acute Bronchopulmonary Suppuration: Therapy with Endoscopic Application of Oleaginous Penicillin*

A. Albert Carabelli, M.D., F.A.C.P., F.C.C.P.†

TRENTON, N. J.

Acute bronchopulmonary suppuration may be considered a pathologic entity which presupposes a block of the bronchus to the bronchopulmonary segment associated with the products of suppuration within the bronchus as well as the parenchyma of the segment. Since the literature on this subject shows a considerable amount of confusion in terminology with many names used for this entity, it is suggested that this disease be called *acute, suppurative, segmental bronchopneumonitis, obstructive in type.* Such a classification is in harmony with the clinical as well as radiologic and bronchologic aspects of this disease.

Clinically the condition is recognized as an acute illness which is associated with chills, fever of the septic type, cough and expectoration, pleuritic pain, dyspnoea, and hemoptysis. Malaise and the usual concomitants of systemic toxemia are also encountered. Pleuritic pain, dyspnoea, and hemoptysis may be present. In some patients the symptoms may be extremely mild, and the condition discovered on routine films following a lower respiratory episode. The physical signs usually consist of dullness and the presence of râles; on the other hand, they may be entirely absent if the segment is deep and not approachable by the usual methods of physical examination. If an associated pleuritis occurs, the signs of an effusion are present and leukocytosis is usually found, as well as an accelerated sedimentation rate. The process is not necessarily confined to the dependent portions of the lungs on

*Read at the First International Congress of Bronchoesophagology in Rio de Janeiro, Brazil, August 24 to 30, 1952.

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the gravitational theory, but no bronchopulmonary segment may be specifically spared.

Diagnosis is made by an evaluation of the clinical symptoms and signs; the roentgen film in several projections; and the bronchoscopic findings. Characteristically the bronchoscopic examination will reveal a fairly normal mucosa with the presence of pus in the affected bronchopulmonary segment, though at times the pus will not be in evidence except after aspiration. Smears of the secretions will show pure pus with occasional normal cellular epithelial elements. Organisms may be found on direct smear and, when present, the pneumococcus is dominant.

Interest in the method of therapy about to be described began with the advent of the antibiotic aerosols, which used the lung as a new therapeutic portal for bronchopulmonary suppurations. While doing bronchograms the author noted the similarity between the viscosity of lipiodol and oleaginous penicillin, both of which had the same basic medium—an organic oil. Another peculiar property of lipiodol observed was its ability to remain in the alveoli for long periods of time without producing local reactions. No focal areas of atelectasis or irritative phenomena accompanied its use. On the premise that oleaginous penicillin should theoretically behave much the same as lipiodol, experiments were conducted with penicillin preparations stained with Sudan III. Of course the penicillin could not be detected by x-ray methods, but its loss (through expectoration) could be easily noted by intelligent patients. Small quantities produced no ill effects, either locally or systemically, and the quantity was therefore increased to 2 cc. and even 3 cc. No irritative phenomena were noted, and the tolerance of the patient to such doses was excellent. Here then was a method of focal therapy which permitted the use of 600,000 to 900,000 units of antibiotic directly into a suppurative area with promise that the penicillin would remain in place for long periods of time. This was considered much more rational than the rather weak blood levels obtained by the parenteral route with little guarantee that a therapeutic amount would penetrate into the relatively avascular area of an atelectatic segment. Since such a segment was also devoid of the normal respiratory function, the aerosol route promised even less concentrations of the penicillin for the small amount of nebulum that settled in the mouth of the obstructed bronchus certainly must be infinitesimal.

To apply the penicillin two applicators were designed—one straight and the other curved with Luer-Lok connections. The tips were atraumatic to avoid accidental perforation of the bronchus. With the bronchoscope in place, the segment involved is identified and aspirated as completely as possible of purulent material. Following this the penicillin is gently instilled directly into the bronchus. The amount used was arbitrarily determined and usually consisted of 2 to 3 cc. representing 600,000 and 900,000 units respectively. It was found best not to irrigate the area with saline solution since the penicillin made a watery emulsion, which was easily lost by coughing; whereas, when introduced directly following aspiration of pus, it remained in situ for long periods of time. This can be shown if the preparation is stained with Sudan III. Expectoration of orange colored sputum indicates loss of penicillin.

The series of patients so treated consisted of 10 adults with the classical findings

of bronchopulmonary suppuration as described above. One had an associated basal effusion which complicated the primary diagnosis. Another had a typical basal segmental lesion with the usual clinical concomitants but on aspiration showed pus teeming with tubercle bacilli. The mucosa of this patient was crimson red in contradistinction to the relatively normal mucosa seen in other patients. The clinical course of this patient paralleled that of the others, though later she was treated as a tubercular. The lesions were anatomically located as follows: right upper lobe, 3; right middle lobe, 3; right lower lobe, 2; left upper lobe, 0; left lower lobe, 2.

In the more severely ill patients, parenteral antibiotics were continued in spite of the fact that their use over a period of one to four weeks prior to the endobronchial instillation had been ineffective. It was felt that the addition of a high blood level would give a further therapeutic boost and possibly prevent spread into normal segments. Five patients received parenteral antibiotics daily, following the bronchoscopic instillation, and 5 patients were given no adjuvant therapy whatsoever.

It was remarkable to see the almost immediate improvement both in the temperature, as well as in the cough and expectoration of each of the patients so treated. At times a rather dramatic result was noted in one to two days. In most cases the temperature dropped to almost normal the day following the endobronchial instillation. Three cases had a slow temperature drop, which took a week to become normal. Two of these required a second aspiration and instillation. The morbidity as judged by the temperature was never longer than one week in any of the series. Roentgen ray evidence showed clearing of the involved segment in one week in most cases; in a few it took two weeks; and in the more severe involvements three weeks. The reversion of the sedimentation rate to normal grossly paralleled the time required for the x-ray picture to clear. The amount of secretions, or their type, apparently had no bearing on the severity of the lesion. One patient with 15 cc. of purosanguenous secretions had a clear x-ray in one week, and the acute symptoms had subsided in two days. On the other hand, a patient with only 2 cc. took one week before she was temperature free and three weeks to clear the x-ray. Follow-up bronchograms were done on 6 patients, and definite mild segmental bronchiectasis was noted in 1 case.

SUMMARY

1. The clinical entity of acute bronchopulmonary suppuration in the light of its clinical, x-ray, and bronchoscopic manifestations is better classified as *acute suppurative segmental broncho-pneumonitis, obstructive in type*.

2. Antibiotic therapy via aerosol or parenteral routes has not been particularly effective in the treatment of this disease in the author's experience.

3. A new method of endobronchial instillation of oleaginous penicillin into the diseased segment as well as the instruments required are described.

4. A series of 10 patients with acute suppurative segmental bronchopneumonitis, obstructive in type, in whom this method has been used with rather dramatic results is reported.

5. Early therapy of acute suppurative segmental bronchopneumonitis with endobronchial oleaginous penicillin provides a specific approach to the treatment of this entity as well as a powerful prophylactic measure for the prevention of its chronic sequelae.

SUPURACION BRONCOPULMONAR: TRATAMIENTO POR MEDIO DE LA ADMINISTRACION ENDOSCOPICA DE PENICILINA OLEOSA

El material estudiado consiste en un grupo de pacientes colectado en un periodo de cinco anos y presenta algunos aspectos interesantes de esta entidad. El tratamiento descrito consiste en la aspiración endoscópica del bronquio afectado, irrigación con solución salina e intilación de preparaciones conteniendo penicilina (en aceite, cera de abejas o suspensiones oleosas) en las regiones enfermas. Este método se ha probado más definitivo en sus resultados y superior al tipo de terapeutica usual con antibióticos, incluyendo los aerosoles de penicilina; puesto que el ataque es directo al foco infeccioso y las altas concentraciones del antibiótico instilado permanecen in situ durante muchos dias. Este método ha disminuido notablemente la morbilidad en los casos médicos y se ha mostrado ser muy valioso en la preparación properatoria de los pacientes que siendo malos riesgos quirúrgicos tienen que someterse a lobectomias, etc., debido a procesos pulmonares supurantes, tales como bronquiectasias. Tambien se describen los instrumentos especiales desarrollados para la práctica de esta técnica.

TRAITEMENT DE SUPPURATIONS BRONCHOPULMONAIRES PAR L'APPLICATION ENDOSCOPIQUE D'UNE SOLUTION HUILEUSE DE PÉNICILLINE

Le travail de cet auteur est basé sur des études faites sur un groupe de patients suivis pendant une période de plus de 5 ans, et présente des phases intéressantes de cet entité.

Le traitement consiste à aspirer la brosche atteinte, à la laver avec une solution salée et à instiller des solutions de pénicilline (huile et cire d'abeilles, ou suspensions huileuses) dans les régions atteientes. Cette méthode fut démontrée plus efficace et supérieure aux modes habituels de traitement, même à la pénicilline en aérosols, en autant qu'on peut atteindre directement le foyer d'infection et que de fortes doses de l'antibiotique soient injectées et demeurent in situ pendant plusieurs jours. Cette méthode a notablement réduit la morbidité dans les ces médicaux ordinaires. Sa valeur est inestimable dans la préparation pré-opératoire de patients d'un pauvre choix pour lobectomie, etc., à cause du processus suppuratif, y compris la bronchectasie.

Description des instruments spéciaux dessinés pour cette technique.

ABSTRACTS

otology

1. *Secretory Otitis Media.* IRVIN HANTMAN, Washington, D. C. Bull. New York Acad. Med. 28:817–26, December, 1952.

The symptom complex of secretory otitis media, with the presence of an effusion in the tympanic cavity, has created much interest among otologists—both because an increased awareness of this condition has resulted in more frequent diagnoses, and also that there has been seemingly a marked increase in the incidence of this disease. There is a possibility that the increase of virus infections and the attenuating effects of the antibiotics may be factors involved in the more frequent formation of serous or mucous secretions within the middle ear. The process must be assiduously searched for in children, for here is an opportunity for reversing pathology before permanent changes render the processes irreversible with permanent hearing damage.

A classification of the disease according to its amenability to therapy into acute, subacute, and recurrent types is offered, in which consideration is given to the various modes of therapy. These range from expectant treatment in the hope of spontaneous resolution, combined with inflations, to removal of the contained secretion by aspiration or myringotomy. The troublesome aspect of some of these cases is due to the tendency in many instances for frequent recurrences to appear, sometimes so severe that we can do little to control them. It is these recurrent types, so puzzling in their nature, that make this disease so bothersome to handle. We have as yet found no uniform satisfactory answer to this form of the disease—besides trying to create a permanent fistula, a difficult and unsatisfactory procedure at best.

Treatment of local pathology that might cause chronic obstruction of the eustachian tube is obviously an important step. The upper half lymphoid elements of Waldeyer's ring must be removed if obstructive, either by surgery, radium, or x-ray therapy. Systemic causes as endocrine disturbances or specific allergies must be investigated and treated. Hilger has offered the extremely interesting

speculation that an autonomic nervous system dysfunction may cause what may be considered a vasomotor otitis media, and based on this theoretical consideration—drugs influencing the autonomic nervous system as Banthine, nicotinic acid, and intravenous histamine, and procaine—may offer a solution to this difficult problem.

Further study of secretory otitis media is necessary, for there are many unsolved aspects of this problem. It is apparent that a more thorough understanding of the mechanism of this interesting disease, will materially aid in the solution of that old but important problem—chronic middle ear deafness.

2. *Recruitment and Speech Discrimination Loss.* HENK C. HUIZING AND J. A. REYNTJES, Groningen, Netherlands. Laryngoscope *62*:521–27, May 1952.

Dutch speech audiometry using Groningen P. B. lists revealed three types of articulation curves: C-type (pure conduction deafness); P-type (perception deafness); and R-type, which is characterized by a kind of resonance hump (chapeau de gendarme) could be related to the subjective distortion caused by recruitment.

The variable type of discrimination loss embodied in this R-type can be defined by two parameters: the minimum discrimination loss D and the half way width H. In connection with the constant type of discrimination loss (P-type) three kinds of hearing impairment are considered: (a) complete drop out of a part of the gamut, (b) subjective masking, (c) tonal dispersion.

The influence of objective and subjective distortion on the articulation curve is discussed. The subjective distortion may be of purely physiologic as well as of pathologic origin.

Peak clipping and automatic volume control do not compensate for subjective distortion; by means of band clipping the center of intelligibility can be moved sometimes to a part of the gamut in which the subjective distortion can be neglected.

The average optimum listening level of 30 db may provide a useful figure for auditory training of young children whose impairment is characterized by the recruitment phenomenon. 9 references. 1 figure.—*Author's abstract.*

3. *Otitis Media: The Practitioner's Responsibility.* W. D. CHASE, Bethlehem, Pa. St. Luke's Hospital Bulletin *7*:7–9, May, 1952.

Before the advent of "the miracle drugs," the practitioner had a more realistic approach toward otitis media than he now has. Then, the classical course, with its earache, headache, fever, tenderness, swelling and fluctuation over the mastoid, demonstrated to the general physician that active and advancing inflammation existed deep in the mastoid and that, unless the diseased mastoid cells were eradicated surgically, intracranial complications impended.

Nowadays, the family physician is guided largely by the pain the patient complains of. He gives "a shot," or two, maybe three, of penicillin and this often

eliminates the pain, since it stops the multiplication of the infecting organisms. However, it does not eliminate the germs and the inflammation continues smoldering on in the depths of mastoid, threatening to break through the paper-thin floor of the cranium or the unclosed petrosquamosal suture, causing meningitis, thrombosis of sigmoid sinus or brain abscess. Very frequently, these ears relapse a little later, another attack occurring. It is my experience that the "stop-and-start" ear comes to mastoidectomy, as a rule.

Since the family physician or the pediatrician sees the patient first, his is the responsibility, largely. Unless prompt drainage and intensive medication are instituted, there is neglect. The drum membrane should be promptly incised, the patient put to bed, particularly if he is a child, and large enough dosage of the chosen medicament given. The presently required dosage of penicillin is 300,000 to 1,000,000 units, given five times a day. Determined specific antibiotic is desirable. The injections must be continued a few days after the pain or discharge stops in order to prevent recurrence and complications.

To provide the patient greatest degree of skilled treatment during the attack and to furnish the auxiliary treatment, reincision if needed, inflation during convalescence to prevent adhesion of drum membrane to the inner wall of middle ear with its damage to future hearing, the skilled otologist should have the care of these cases, if not fully, at least as continuing consultant. —*Author's abstract.*

4. *Local Injection of Procaine Penicillin Solution in Secondary Mastoiditis.* SIMON L. RUSKIN, New York, N. Y. Eye, Ear, Nose & Throat Monthly *31*:36-37, 50, January 1952.

Among the many dramatic experiences in medicine today is the gratifying one of local injection of procaine penicillin solution of 3,000 to 5,000 units per cc. directly into the inflamed and abscessed areas. It may be considered as dramatic when Arentsens reporting on 87 cases of a variety of suppurative infections, concluded "it is only necessary to use one single injection, or at the outside, in order to complete the cure in a very acute inflammatory process, we use two." He quite correctly stated that the pain, which is the fundamental symptom for the patient, disappears promptly and only reappears in a very diminished form in less than 20 per cent of the cases.

Arentsens was also impressed by the obvious fact that 5,000 units of procaine penicillin locally into the infected area produced an antibiotic level at the desired point that millions of units could not accomplish by systemic therapy.

In this paper a striking example of this fact was demonstrated by the case of Dr. R. S., a research physician, age 19. The patient was brought in from the country with an acute left secondary mastoiditis with the mastoid area filled with a red, tender, fluctuating mass which was typical of the variety that in previous years was incised and drained and a fresh mastoid curettement done. The patient was running a temperature of 101° and suffering intense pain so that sleep had been difficult even with sedation. Injection of 2 cc. of procaine penicillin solution,

5,000 units per cc. directly into the core of the inflamed area was followed both by immediate relief of pain and rapid resolution of the abscess within 24 hours. Following the second injection the patient had recovered sufficiently to feel that he could return to his home upstate. Uneventful absorption of the abscess followed with complete recovery. A third injection was administered although it was not strictly necessary. The use of procaine penicillin solution 5,000 units per cc. for surgical anesthesia in tonsillectomy and nasal surgery was reported in a previous paper. 5 references.—*Author's abstract.*

5. *Further Observations Concerning the Toxic Effects of Streptomycin and Quinine on the Auditory Organ of Guinea Pigs.* L. RUEDI, W. FURRER, F. LUTHY, G. NAGER, AND B. TSCHIRREN, Zurich, Switzerland. Laryngoscope *62*:333–51, April 1952.

The protracted administration of streptomycin to guinea pigs produces in them a marked functional disturbance of equilibrium and a reduction in sound perception. Previously described changes in the nuclear area of the acoustic nerve were again observed; however, they seem not to be specifically due to streptomycin. According to our findings, the vestibular dysfunction is mainly associated with degeneration of the sensory terminals of the peripheral vestibular system as described by R. Caussé and K. Berg; and the cochlear functional losses are correlated to a degeneration, most pronounced in the lowest cochlear turns, of the organ of Corti with its associated nervous system and of the stria vascularis.

Prolonged administration of large doses of hydrochloric quinine to guinea pigs provokes marked loss of sound perception, and this is histologically related to the organ of Corti and stria vascularis degeneration which together with pathologic changes of the stria vascularis extend over several cochlear turns. These degeneration processes originated by quinine begin in the external hair cells as shown by Covell.

We regret that Raoul Caussé did not live to enjoy this confirmation of his experiments on experimental streptomycin lesions of the ear. 12 references. 12 figures.—*Author's abstract.*

6. *Ménière's Syndrome as a Premonitory Symptom of Cerebrospinal Vascular Occlusion: A Report of Two Cases.* WILLIAM G. ENSIGN, Minot, North Dakota. Ann. Int. Med. *36*:1167–72, May 1952.

Two cases are presented in which the initial illnesses were indistinguishable from Ménière's Syndrome but whose final diseases were occlusions of the posterior inferior cerebellar artery (Wallenberg's Syndrome). In one case a 67 year old man presented vertigo, nausea, vomiting, nystagmus, and diminished hearing for six days. He suddenly lapsed into coma which lasted several days. Upon recovery the neurologic syndrome of an occlusion of the posterior inferior cerebellar artery became evident. On the right side of the body there were miosis, enophthalmos, ptosis of the eyelid, paralysis of the palate and pharynx, and hypalgesia of

the face. Over the left side of the body there was hypalgesia to pinprick. Complete recovery occurred over a four week period.

The second case was a 59 year old woman with diabetes mellitus who presented vertigo, nausea, vomiting, nystagmus, and tinnitus of two weeks' duration. There was then a sudden onset of semicoma, dysphagia, numbness of the left arm, anisocoria, profuse sweating only over the left half of the face, ptosis of the right eyelid, hypalgesia over the right side of her face and the left arm, and complete paralysis of the right palate. The patient died eight hours later, the autopsy showing a thrombotic occlusion of the right vertebral and right posterior inferior cerebellar arteries.

There are very few references in the literature which bring out any relationship between these two entities and yet as experienced in these cases the clinical picture was confusing. And by the same token Ménière's Syndrome is not always an easy diagnosis and it should be made only after the exclusion of other diseases. 12 references.—*Author's abstract.*

7. *Deafness—Its Present Day Management.* ARTHUR L. JUERS, Miami, Fla. J. Kentucky M. A. *50*:198–205, May 1952.

The author discusses in particular the forms of deafness which can be benefitted by medical or surgical treatment. Central perforations of the tympanic membrane can frequently be closed by local treatment as outlined in the article. The majority of closures will improve the hearing significantly. The importance of allergy as an etiologic factor in chronic secretory otitis media and recurrence of lymphoid tissue in the nasopharynx is stressed. A high percentage of cases of deafness due to clinical otosclerosis can be rehabilitated by fenestration surgery.

Congenital deafness is classified on the basis of etiology into endogenous and exogenous types. Endogenous deafness is the result of a true genetic defect. The exogenous group includes those cases which have normal genetic background but in which the developmental process is upset by such conditions as prenatal German measles or kernicterus from Rh incompatibility.

Cochlear hydrops without involvement of the labyrinth is occasionally a cause of deafness. Features of this deafness are its usual fluctuating character, greater loss for the lower frequencies, low-pitched tinnitus and diplacusis. Treatment is directed toward elimination of the excess cochlear fluid and release of the local vasospasm. 24 references. 10 figures.—*Author's abstract.*

8. *Deafness Following Mumps: Rehabilitation.* ARTHUR J. COOMBS, Chicago, Ill. Laryngoscope *62*:204–10, February 1952.

The author points out that 3 to 5 per cent of the cases of acquired deafness are due to mumps, although less than 1 per cent of the cases of mumps show evidence of impaired hearing. It is probable that many cases of nerve deafness of unknown etiology in children are due to mumps.

The symptoms may vary from a mild sense of fullness, slight tinnitus, or even mild earache to severe labyrinthine disturbance followed by either unilateral or bilateral deafness.

He reports the case of a 36 year old female, a private secretary, who had such a stormy case, bilateral in onset, with partial recovery on one side and practically no residual function on the other. After the symptoms had subsided to the maximum degree she was fitted with a hearing aid suspended high on the right side of her chest so that the telephone receiver could be held over it and the transmitter would be in the usual position for speaking. An amplifier was installed on the telephone at her desk and in her home. She is now able to carry on her work as efficiently as before her illness.

The author also emphasizes the importance of cooperation between employer and employee. Psychotherapy may be necessary to inspire the patient with a desire to overcome his handicap and lip reading is essential for complete rehabilitation. 11 references. 2 figures.—*Author's abstract.*

9. *Ventriculomastoid Shunt in the Management of Obstruction to the Aqueduct of Sylvius in the Adult: Report of Case.* HENDRIK J. SVIEN, HENRY W. DODGE, JR., AND CLIFFORD F. LAKE, Rochester, Minn. Proc. Staff Meet., Mayo Clin. 27:215–18, May 21, 1952.

The procedure of shunting cerebrospinal fluid from the lateral ventricle of the brain into the mastoid antrum has been modified by various workers. The modification which the authors have used consists of inserting one end of a polythene tube into the posterior horn of the lateral ventricle through a burr-hole opening made in the parietal bone. The other end of the tube is then passed subcutaneously into the region of the mastoid process and inserted into the mastoid antrum through an opening made through the cortex of the mastoid bone.

The procedure which the authors have outlined is said to have the advantage of low risk and simplicity. It can be carried out under local anesthesia in the critically ill patient. Another advantage of this procedure is that if cerebrospinal fluid ceases to drain, the shunt can be explored easily and the tube reinserted at either the ventricular or antral site. Electrolyte balance is not disturbed, since the cerebrospinal fluid passes through the eustachian tube and is swallowed and returned to the body economy through the gastrointestinal tract.

The authors say that this procedure probably will find its greatest use in cases of internal hydrocephalus due to severe adhesive arachnoiditis of the posterior fossa and basal cisternae. In these instances, neither the Torkildsen procedure nor third ventriculostomy can be used, because the sites for reabsorption of the cerebrospinal fluid no longer exist. In these cases, the fluid must be diverted from the brain to some other body cavity, and at the present time, this procedure of ventriculomastoid shunt seems the most feasible in accomplishing this end. 1 reference. 2 figures.—*Author's abstract.*

laryngology

10. *Progress in the Surgical Treatment of Bilateral Laryngeal Paralysis.* THOMAS M. EDWARDS, Tampa, Fla. Ann. Otol., Rhin. & Laryng. *61*:159–78, March 1952.

A comprehensive survey of the subject of bilateral recurrent laryngeal paralysis, clinically known as bilateral abductor paralysis of the larynx, is presented in this successful candidate's thesis to the American Laryngological, Rhinological & Otological Society. Not too well understood, the condition may be overlooked; in addition, it is dangerous if not diagnosed promptly and treated properly, for respiratory infection may increase obstruction of the airway sufficiently to cause asphyxiation, or, if the paralysis is not taken into consideration, the patient may become asphyxiated if subjected to anesthesia. Particularly is the evolution of the surgical therapy of this relatively infrequent but deplorable affliction delineated in some detail.

Incidence, etiology, and symptoms are described. It is emphasized that among the numerous causes of bilateral recurrent laryngeal paralysis, trauma resulting from thyroidectomy is by far the commonest cause. The outstanding symptoms are dyspnea and inspiratory stridor in varying degree with loss of voice. At first, relaxed in the cadaveric position, the cords are drawn closer together as fibrosis and contractures take place, so that six months to a year may elapse between paralysis and pronounced obstructive dyspnea.

The surgical measures from tracheotomy through cordotomy, cordectomy, ventriculocordectomy and anastomosis of the recurrent nerves to the constructive extralaryngeal procedures of the last decade are traced, and the King procedure and the Kelly procedure, whose introduction in the early forties brought about a renaissance of interest in the correction of this deplorable state, are described and compared. Also reviewed are various modifications of these well known procedures.

A detailed description of the new Thornell intralaryngeal approach is presented. This operation is based on the use of the Lynch suspension laryngoscope and consists of complete intralaryngeal arytenoidectomy with lateral fixation of the corresponding vocal cord. The modifications of this procedure advocated by von Leden and Brown are also described. Two cases are reported in which the Thornell operation with the Brown modification was employed with gratifying results.

The intralaryngeal approach is recommended for its simplicity. As yet, however, it is not possible to have the best airway with the best voice. While the eventual method of choice appears to remain problematic, it is suggested that selection of the operative procedure may be determined on an anatomic basis. The intralaryngeal procedure may prove most suitable for patients with a large larynx, while for those with a small larynx the extralaryngeal procedure may be preferable.

To reduce the incidence of bilateral laryngeal paralysis as a sequela of thyroidectomy, it is urged that the precautions long stressed in the literature be scrupulously observed, namely, careful examination of the larynx before thyroid surgery, and routine dissection and demonstration of the recurrent laryngeal nerves at the time of surgery. 61 references.—*Author's abstract.*

11. *Left Recurrent Laryngeal Nerve Paralysis in Arteriosclerotic Heart Disease.* S. ZELMAN AND G. W. NICE, Topeka, Kan. J. A. M. A. *149*:1291–93, August 2, 1952.

Hoarseness due to left recurrent laryngeal nerve paralysis is a rare occurrence in patients with congestive heart failure of any cause but is most commonly seen with severe mitral stenosis, and less commonly with congenital heart disease, when marked dynamic dilatation of the left pulmonary artery compresses the nerve against the aortic arch, its adjacent lymph nodes, and the ligamentum arteriosum. It is extremely uncommon in patients with arteriosclerotic heart disease, a case of which is reported.

The rarity of compression of the recurrent nerve in arteriosclerotic heart disease as compared with mitral stenosis is explained by the fact that the left ventricle of the heart bears the primary cardiac strain, sparing the pulmonary circulation, and when left ventricular failure finally occurs it is apt to be of relatively rapid onset or intermittent in character, so that the right ventricle does not, as in patients with mitral stenosis, enjoy a prolonged period of adjustment to a state of pulmonary hypertension. The more rapid failure of the right ventricle then relieves the pulmonary hypertension which is responsible for dynamic dilatation of the pulmonary arteries.

The patient reported resembled cases with mitral stenosis in that he had left ventricular failure with pulmonary congestion and right heart strain for nearly four years without experiencing right heart failure. An unusually low transverse aorta encroaching on the "aortic window" may have contributed to cause the nerve compression. 6 references. 2 figures.—*Author's abstract.*

12. *An Afferent Representation of the Larynx in the Cerebellum.* ROBERT L. LAM AND JOSEPH H. OGURA, St. Louis, Mo. Laryngoscope *62*:486–95, May 1952.

Stimulation of the proximal end of the cut superior laryngeal nerve in the cat by single shocks resulted in evoked potentials recorded by the cathode ray oscilloscope. Such potentials were recorded from remarkably discrete areas of the cerebellum bilaterally including crus I and the third and fourth folia of the paramedian lobule. Latency was usually between 20–30 msec. Responses reached up to the millivolt in amplitude. The threshold necessary to produce the cerebellar responses corresponds to that assignable to the "A" action potential of the superior laryngeal nerve. It was concluded that the cerebellum participates as an afferent center in laryngeal functions. 6 references. 3 figures.—*Author's abstract.*

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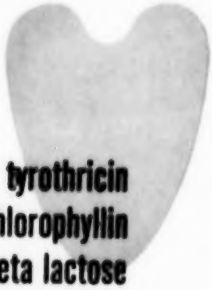

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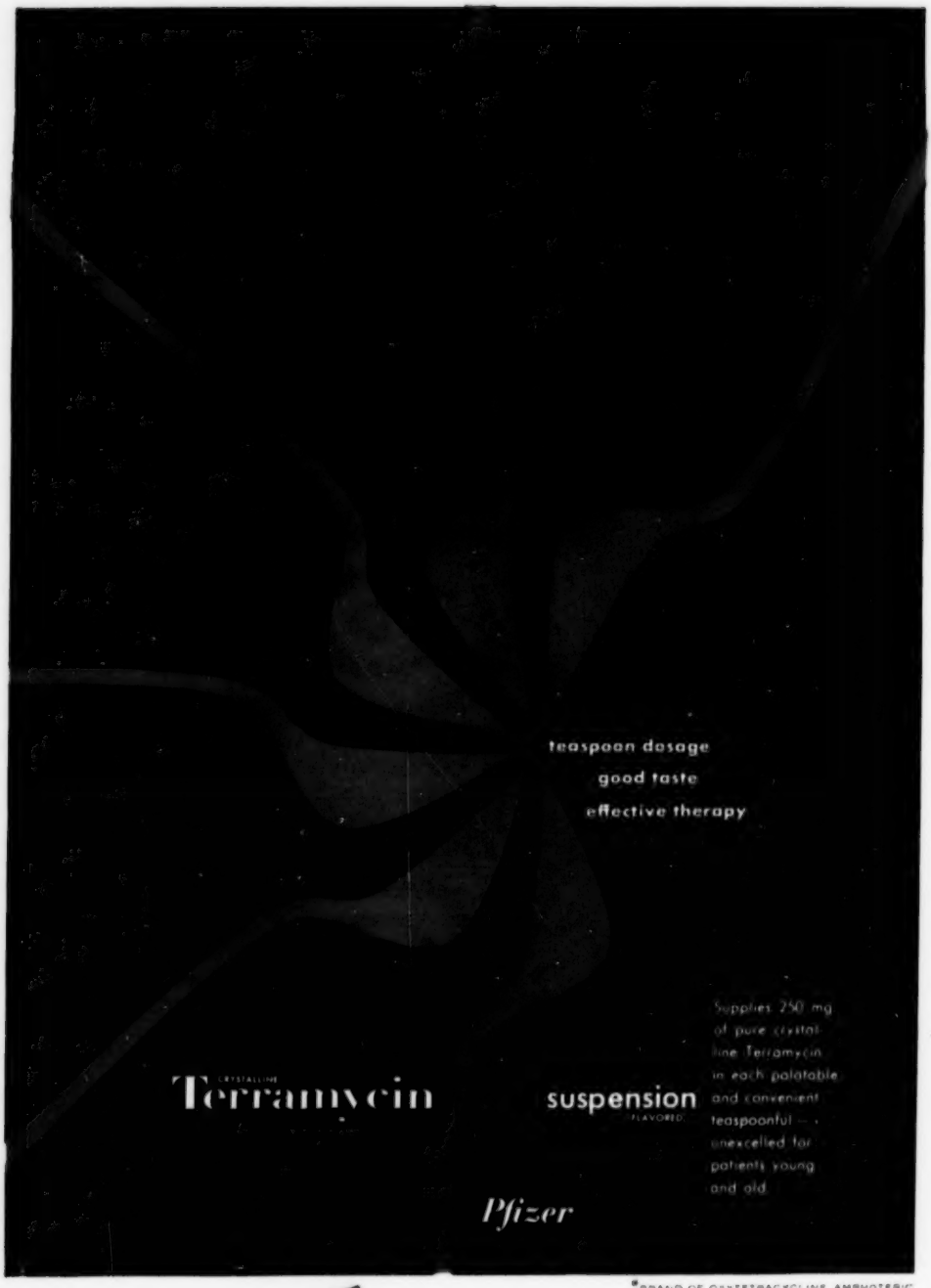

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